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(54) EXTERNAL PREPARATION

(57)Abstract:

PURPOSE: To obtain an external preparation, containing a specific compound eliminating single oxygen, capable of preventing collagen from causing the cross-linkage-forming reaction, the instantaneous blackening from occurring, enzymes from being inactivated, etc., and thereby suppressing the aging and utilizable as cosmetics and medicines.

CONSTITUTION: This external preparation is obtained by blending a compound such as α -glucosylrutin, hypotaurine, thiotaureine or phosphatidyl-choline having $\geq 1 \times 10^6 \text{ mol}^{-1} \text{ sec}^{-1}$ rate constant of reaction with single oxygen in an amount of 0.0001–10% (preferably 0.001–1%) therein. Furthermore, the external preparation is preferably combined with an ultraviolet light absorber such as 4-t-butyl-4'-methoxydibenzoylmethane or sodium hydroxymethoxybenzophenonesulfonate.

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CLAIMS**[Claim(s)]**

[Claim 1] the collagen bridge formation inhibitor which contains the compound whose velocity constant with singlet oxygen is more than $1 \times 10^6 M^{-1}s^{-1}$ as an active principle, and instance -- melanism -- the external preparations chosen from an inhibitor, an enzyme deactivation inhibitor, or a coloring matter tenebrescence inhibitor.

[Claim 2] Furthermore, external preparations given [containing an ultraviolet ray absorbent] in the 1st term of a claim.

[Claim 3] The 1st term of a claim which is a charge of makeup, or external preparations given in the 2nd term.

[Translation done.]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]**[0001]**

[Industrial Application] About external preparations, this invention prevents melanism, enzyme inactivation, etc. the arch-forming reaction of a collagen, and instantly, as a result controls aging in more detail, and relates to the external preparations used as cosmetics or physiotherapy.

[0002]

[Description of the Prior Art] In recent years, various diseases by active oxygen attract attention, and active oxygen has been said whether to involve also to aging. Super oxide, a hydroxy radical, a hydrogen peroxide, and singlet oxygen are contained in active oxygen, and the resultant with these metals and lipids is also known as active oxygen of a wide sense.

[0003] Various external preparations are studied in order to prevent various diseases in which active oxygen participates. For example, although the collagen which is a dermis constituent is bearing the resiliency of the skin, and flexibility, if bridge formation is formed in this collagen, resiliency and flexibility will fall, it is supposed that it is the cause of aging of the skin, and the collagen bridge formation inhibitor for preventing such a phenomenon is examined. moreover, the delayed type according to UV-B in the melanism by ultraviolet rays -- the instance for existence of melanism being known the instance by UV-A besides melanism, and preventing such melanism -- melanism -- the inhibitor is examined.

[0004] Furthermore, the enzyme deactivation inhibitor for many enzymes which are bearing the reaction in the living body to prevent deactivation of the ***** cages in which the rate of deactivating with advance of aging becomes high, and the restoration becomes difficult, and these enzymes are examined. Furthermore, although the tenebrescence of coloring matter, such as vegetable extractives, or discoloration included in the charge of makeup etc. may become the stability top problem of cosmetics again and this cause is set to light, temperature, and pH, explanation does not attach all so then and the drugs which prevent ** and discoloration of coloring matter are examined.

[0005] The above-mentioned collagen arch forming and instance, although it was admitted that active oxygen was participating in phenomena, such as melanism, enzyme deactivation, and coloring matter tenebrescence, it was not known about these actual cause or its action mechanism, but, as for the compound effective in prevention of each [these] phenomenon, it was actual to have found out experientially and to have not spread.

[0006]

[Problem(s) to be Solved by the Invention] Therefore, it searched for causes including the action mechanism about the above-mentioned phenomenon, and offer of the external preparations which can prevent these phenomena was called for.

[0007]

[Means for Solving the Problem] Although each of these phenomena had very high reactivity among active oxygen as a result of this invention persons' examining synthetically what kind of active oxygen is involving about melanism, enzyme deactivation, coloring matter tenebrescence, etc. the above-mentioned collagen arch forming and instance, the life was very short and its attention was paid to possibility that the singlet oxygen by which the concrete effect to a living body, for example, the skin, is not known is involving.

[0008] However, about singlet oxygen, he has noticed that the matter which there is no method of still detecting this correctly, cannot grasp relation of the various phenomena on the skin as singlet oxygen correctly, as a result eliminates this cannot be found out correctly.

[0009] Then, this invention persons inquired about the detection approach of singlet oxygen first, and developed new singlet oxygen detection equipment. Subsequently, the place which searched the matter which eliminates an operation of singlet oxygen and singlet oxygen with this detection equipment, Arch forming of the collagen which is the major component of dermis which is made into the failure by active oxygen in the living body, as a result leads to aging, As for the compound more than fixed, things already caused by beam singlet oxygen, such as deactivation of various enzymes indispensable to melanism and a living body instance which happens nonenzymatic by oxidation of dopa, and a reaction constant with singlet oxygen completed a header and this invention for the ability of these failures to be controlled effectively.

[0010] namely, the collagen bridge formation inhibitor with which this invention contains the compound whose velocity constant with singlet oxygen is more than $1 \times 10^6 M^{-1} s^{-1}$ as an active principle and instance -- melanism -- the external preparations chosen from an inhibitor, an enzyme deactivation inhibitor, or a coloring matter tenebrescence inhibitor are offered.

[0011] a velocity constant with the singlet oxygen used in this invention can excite a photosensitizer by the laser radiation of the equipment which these people developed, i.e., ultraviolet-rays wavelength, and can choose easily the compound beyond $1 \times 10^6 M^{-1} s^{-1}$ (henceforth a "singlet-oxygen elimination compound") by using the equipment (Japanese Patent Application No. No. 340377 [five to]) based on the principle of detecting near-infrared luminescence which the generated singlet oxygen gives off.

[0012] If it says in more detail, the laser of ultraviolet-rays wavelength can be irradiated at the system by which generating of the singlet oxygen by photochemical sensitization is known, fine luminescence of the specific near-infrared section can be measured to singlet oxygen, luminescence when subsequently adding a sample compound to the same system can be measured, it can ask for a velocity constant with singlet oxygen from reduction of the near-infrared section luminescence, and, thereby, a singlet oxygen elimination compound can be screened.

[0013] Calculation of a concrete velocity constant (kq) should just ask for ratio (I_0)[of luminescence reinforcement (I_0) when not adding the singlet oxygen elimination agent / as opposed to the luminescence reinforcement at that time (I) for the concentration (C_q) of a sample compound (singlet oxygen elimination agent) / to the X-axis $J/(I)$ by the formula of Stern-Vormer, and $I_0/I = 1 + kq \cdot \tau - C_q$ from these relation for a Y-axis. In this formula, tau is the life of singlet oxygen and is a constant which changes with solvents.

[0014] As an example of the singlet oxygen elimination compound found out by this approach, what is shown, for example in degree table is mentioned.

[0015]

表 1

物質名	反応速度定数 (M ⁻¹ s ⁻¹)
β-カロチン	7.0×10 ⁹
α-グルコシリルチ	6.1×10 ⁹
ルチン	5.5×10 ⁹
ヒスチジン	5.4×10 ⁹
キノリン	1.0×10 ⁹
ドデシル硫酸ナトリウム	1.0×10 ⁹
アジ化ナトリウム	7.9×10 ⁸
α-トコフェロール	7.1×10 ⁸
クロロフィルa	7.0×10 ⁸
ドーパ	6.8×10 ⁸
β-トコフェロール	3.6×10 ⁸
トリプトファン	2.5×10 ⁸
γ-トコフェロール	1.9×10 ⁸
カテキン	0.6~1.2×10 ⁸
ケルセチン	1.1×10 ⁸
ケルセチン脂肪酸エステル	5~8×10 ⁷
δ-トコフェロール	7.1×10 ⁷
ハイドロキノン	6.9×10 ⁷
ナフトール	0.7~3.2×10 ⁷
ルミノール	3.0×10 ⁷
チロシン	2.7×10 ⁷
メチオニン	2.2×10 ⁷
プロアントシアニジン	1.0~2.1×10 ⁷
システイン	1.8×10 ⁷
ビリルビン	1.5×10 ⁷
エルゴステロール	1.3×10 ⁷
アスコルビン酸	8.3×10 ⁶
レチノール	7.3×10 ⁶
チオタウリン	1.1~2.3×10 ⁶
ホスファチジルコリン	2.1×10 ⁶
ヒポタウリン	1.0~2.0×10 ⁶
スクワレン	1.9×10 ⁶
ホスファチジルエタノールアミン	1.6×10 ⁶
酢酸トコフェロール	1.6×10 ⁶
アントラセン	7.4×10 ⁵
ピペリジン	4.1×10 ⁵
ドコサヘキサエン酸	2.9×10 ⁵
リノール酸	2.2×10 ⁵
オリーブ油	1.5×10 ⁵

オレイン酸	1.3×10^5
インデン	6.7×10^4
コレステロール	6.6×10^4
リモネン	5.9×10^4
安息香酸	5.0×10^4
マンニトール	1.8×10^4

[0016] The external preparations of this invention are manufactured by combining the singlet oxygen elimination compound found out as mentioned above, the well-known basis for ***** agents, or the basis for cosmetics according to a conventional method.

[0017] Generally the loadings of a singlet oxygen elimination compound are 0.0001% - 10% during a presentation, although it changes also with reaction reinforcement with the singlet oxygen of a singlet oxygen elimination compound besides being the dosage forms of external preparations, the purpose of use, etc. What is necessary is just to be 0.001% - about 1% preferably.

[0018] Concretely, the loadings range by the application of a singlet oxygen elimination compound and external preparations is illustrated to the next Table 2 and 3.

[0019]

表 2

化合物名	即時黒化 抑制効果	コラーゲン架橋 抑制効果	酵素失活 抑制効果
α-グルコシル ルチン	0.01~0.1	0.1~1	0.1~1
ドデシル硫酸 ナトリウム	0.01~0.1	0.01~0.1	0.01~0.1
アジ化ナトリ ウム	0.1~1	0.5~2	0.5~2
ドーバ	—	0.1~1	0.1~1
アントシアニン	0.1~1	0.1~1	0.1~1
メチオニン	1~5	1~5	1~5
チロシン	1~5	1~5	1~5
システイン	1~5	1~5	1~5
ヒスチジン	0.01~0.1	0.01~0.1	0.5~2
トリプトファン	0.05~0.2	0.05~0.2	0.5~2
カテキン	0.1~1	0.1~1	0.1~5
ハイドロキノン	1~5	1~5	1~5
プロアント シアニジン	1~5	1~5	1~5
アスコルビン酸	1~5	1~5	1~5
チオタウリン	1~5	2~10	2~10
ヒポタウリン	1~5	2~10	2~10

(A unit is weight %)

[0020]

表 3

化 合 物 名	色 素 褪 色 抑制効果
β-カロチン	0.01~0.1
ルチン	0.01~0.1
キノリン	0.01~0.1
クロロフィルa	0.01~0.2
α-トコフェロール	0.01~0.5
β-トコフェロール	0.01~0.5
γ-トコフェロール	0.01~0.5
δ-トコフェロール	0.01~0.5
ケルセチン	0.01~0.5
ケルセチン脂肪酸エステル	0.01~0.5
ハイドロキノン	0.05~5
ナフトール	0.05~5
ルミノール	0.05~5
ビリルピン	0.05~5
エルゴステロール	0.05~5
レチノール	0.1~5
ホスファチジルコリン	0.1~5
スクワレン	0.1~5
ホスファチジル	0.1~5
エタノールアミン	
酢酸トコフェロール	0.1~5

(A unit is weight %)

[0021] The aquosity component and powder which are used for a usual ***** agent and the usual charge of makeup if needed, a surfactant, oils, a moisturizer, alcohols, pH regulator, antiseptics, coloring matter, an antioxidant, a thickener, perfume, etc. can be further blended with the external preparations of this invention suitably, and it can consider as dosage forms, such as a milky lotion, a cream, face toilet, a pack, ointment, dispersion liquid, and a charge of washing.

[0022] As for the external preparations of this invention, combining with an ultraviolet ray absorbent is desirable, and Para methoxycinnamic acid 2-ethyl ester, 2-hydroxy-4-methoxybenzophenone, 4-t-butyl-4'-methoxydibenzoylmethane, hydroxy methoxybenzophenone sulfonic-acid sodium, etc. are mentioned as an example of such an ultraviolet ray absorbent. Among these, what has big absorption especially in UV-area A, for example, 4-t-butyl-4'-methoxydibenzoylmethane, hydroxy methoxybenzophenone sulfonic-acid sodium, etc. are desirable.

[0023] the singlet oxygen which the external preparations obtained by the above generate on a living body, especially the skin -- effective -- eliminable -- a collagen bridge formation inhibitor and instancey -- melanism -- it is used as an inhibitor, an enzyme deactivation inhibitor, a tenebrescence inhibitor of coloring matter, etc.

[0024] among these, instancey -- melanism -- when using it as an inhibitor, it is more desirable as a singlet oxygen elimination compound that a velocity constant is larger than dopa (6.8×10^8 it is above), but even if it is a compound with a velocity constant smaller than dopa, the same effectiveness can be acquired by carrying out high concentration addition. Moreover, when using as a deactivation inhibitor of an enzyme, it is more desirable that the reaction constant of a singlet oxygen elimination compound is larger than the velocity constant of the enzyme.

[0025]

[Example] Next, although the example of a trial and an example are given and this invention is explained in more detail, this invention is not restrained at all by the example of these trials etc.

[0026] Trial ** Example Measuring method of 1 singlet oxygen : The measuring device of [measuring device []] singlet oxygen was constituted as follows.

(1) Light source section : the argon laser by the coherent (Coherent) company (Innova 70-4)

(2) Intensity modulation section : IntraAction (IntraAction) acoustooptic modulator (ASM-702-8, ME-70)

(3) Flow cell : the flow cell made from a quartz (cel length 3mm; capacity 0.18ml)

[0027] (4) The pump for circulation, and bubbling equipment : peri SUTARU theque pump by the Iwaki glass company A TST-100 high-pressure-oxygen chemical-cylinder (5) light filter, a spectroscope, and a detector: Colored glass filter (IR-80)

The spectroscope by Jasco Corp. (CT-10, slit width of 2mm)

germanium[by the applied detector (Applied Detector) company]-detector (Model 403 HS; liquid nitrogen cooling)

(6) Amplifier EG & G Lock in amplifier by the pudding SETON applied research (EG & G Princeton Applied Research) company (Model(s) 124A and 116)

[0028] As a [measuring method []] test portion, it is hematoporphyrin. 20microM solution was used. This hematoporphyrin solution was circulated at the rate of 20 ml/min among the flow cell.

[0029] Laser with a wavelength (absorption maximum wavelength of hematoporphyrin) of 350-365nm was irradiated at this cel. When this exposure investigated the emission spectrum of the near infrared region to produce, it checked that a peak was in 1268nm. This peak corresponds to transition of an excitation singlet oxygen molecule.

[0030] Subsequently, when the concentration of hematoporphyrin was changed and the luminescence reinforcement of 1268nm was investigated, in low concentration, getting on a straight line mostly was checked and it checked that this luminescence was what is depended on the singlet oxygen generated when hematoporphyrin is made into a photosensitizer.

[0031] Trial ** Example The measurement trial of two reaction rate constants: The reaction rate constant was measured using the rose bengal which is a typical photosensitizer, the alpha-tocopherol as an elimination compound, and each ethanol solution of a quinoline. Laser light was irradiated at each alpha-tocopherol of the rose bengal of 50microM, and 0,100,200,300,400microM, and the mixed solution of a quinoline, and the luminescence reinforcement in 1268nm was measured.

[0032] As shown in drawing 1, the concentration (Cq) of an elimination compound was taken along the axis of abscissa, Io/I (luminescence reinforcement in each concentration when luminescence reinforcement in case the elimination compound of Io is 0, and I add an elimination compound) was taken along the axis of ordinate, and kq (velocity constant) was calculated from the inclination of the obtained graph according to the formula of Stern-Vormer, and $Io/I = 1 + kq \cdot \tau \cdot Cq$. In addition, the life (τ) of the singlet oxygen in the inside of ethanol is 10-12microsec.

[0033] trial ** Example the instancy by 3 photooxidation -- inhibition test [of melanism]: -- first -- 1mM Dopa and 5microM The mixture (phosphate buffer solution; pH7.5) of hematoporphyrin was taken on the petri dish, UV-A 5 mW/cm² was irradiated for 10 minutes by the solar simulator, and it asked for generation of the dopa chromium which changed from dopa by measuring the absorbance of 475nm. Subsequently, the singlet oxygen elimination compound was added to the above-mentioned mixture, and generation of the dopa chromium when irradiating UV-A was investigated. This result is shown in the following table.

[0034]

表 4

一重項酸素消去化合物	濃 度	475 nmの吸光度
α-グルコシルルチン	0.05%	0.08
α-グルコシルルチン + ヒドロキシメトキベンゾフェノン スルホン酸ナトリウム	0.05% + 0.01%	0.06
ヒスチジン	0.05%	0.1
ドデシル硫酸ナトリウム + ヒドロキシメトキベンゾフェノン スルホン酸ナトリウム	0.1% + 0.01%	0.13
ドデシル硫酸ナトリウム	0.1%	0.17
ヒポタウリン	1%	0.2
マンニトール	1%	0.35
安息香酸	1%	0.32
な し (ブランク)		0.38

[0035] Since the singlet oxygen elimination compound with a larger velocity constant than $1 \times 10^6 M^{-1}s^{-1}$ controls generation of dopa chromium, it controls melanism instancy and can serve as an effective singlet oxygen elimination agent, so that clearly from this result, in addition, the thing for which each above-mentioned compound is combined with an ultraviolet ray absorbent -- it is -- generating of singlet oxygen -- stopping -- further -- instancy -- melanism -- depressor effect becomes high.

[0036] Trial ** Example Depressant action of arch forming of four collagens: Add 200microM hematoporphyrin 100microl to about 1mg/ml I-beam collagen 200microl, and add 50 mM Tris-HCl buffer solution so that the whole quantity may be further set to 1ml. This is taken on a petri dish and UV-A 2 mW/cm² is irradiated for 20 minutes by the solar simulator. Under the present circumstances, reaction mixture is ice-cooled and agitated.

[0037] The sample before and behind a UV-A exposure is separated in SDS-PAGE, and change of the amount of alpha of a collagen, beta, and a gamma chain is seen. It compared by the case where variation of alpha of this collagen, beta, and a gamma chain is not added with the case where a sample compound (singlet oxygen elimination compound) is added, and that operation was investigated. This result is shown in the following table.

[0038]

表 5

被検化合物	濃 度	コラーゲンの変化程度
α -グルコシルルチン	0.1 %	UV-A照射前と比べ変化なし
チオタウリン	5 %	同 上
ヒポタウリン	5 %	同 上
ドデシル硫酸ナトリウム	0.1 %	同 上
カテキン	0.1 %	同 上
アジ化ナトリウム	0.5 %	同 上
マンニトール	1 %	高分子側の α 鎖バンドが増え、架橋形成が示された
安息香酸	1 %	同 上
なし (ブランク)		同 上

[0039] When a singlet oxygen elimination compound was added like [it is ***** and] from this result, it was shown that arch forming of a collagen is controlled.

[0040] Trial ** Example 5 ** Base *** *** System : This enzyme solution after 300microl Adding the hematoporphyrin of 200microM to 3ml of 0.5mg [/ml] tyrosinase solutions and carrying out a fixed time amount exposure of UV-A A 3.9ml phosphate buffer solution (pH6.8) is added to 0.1ml.

[0041] Subsequently, dopa of 10mM 1ml was made into the substrate, the amount of the dopa chromium generated in 10 minutes at 37 degrees C was measured with the absorbance of 475nm, and the fall of tyrosinase activity was checked from the fall of the amount of dopa chromium which generates as contrast what does not irradiate UV-A. The tyrosinase activity at the time of adding a sample compound (singlet oxygen elimination agent), and on the other hand, irradiating UV-A was measured, and the depressor effect of tyrosinase deactivation by the elimination agent was investigated. This result is shown in degree table.

[0042]

表 6

被検化合物	濃 度	残存活性 (%)
アジ化ナトリウム	0.5 %	9 8
α -グルコシルルチン	0.1 %	9 8
トリプトファン	1 %	9 7
チオタウリン	5 %	8 2
ヒポタウリン	5 %	8 5
マンニトール	1 %	4 5
安息香酸	1 %	3 9
なし (ブランク)		3 8

[0043] What has a larger reaction constant with singlet oxygen than $1 \times 10^6 M^{-1}s^{-1}$ can control deactivation of the enzyme concerned so that clearly from this result.

[0044] Trial ** Example Six colors Base ** Color ** System Effect ** : Rose bengal 0.01% and Orange Orange after putting II 0.01% of coloring matter mixed liquor into Fl box for two weeks The absorbance of

484nm which shows the maximum absorption of II was measured, and it asked for whenever [tenebrescence / of Orange II]. Subsequently, the sample compound (singlet oxygen elimination compound) was added into the same coloring matter mixed liquor, whenever [tenebrescence / in this case] was measured, and the coloring matter tenebrescence depressor effect of a sample compound was investigated. This result is shown in the next table.

[0045] In addition, coloring matter tenebrescence depressor effect was searched for from the following formula.

$$\text{褪色抑制率} = \frac{\text{試験後の } 484\text{ nmの吸光度}}{\text{試験前の } 484\text{ nmの吸光度}} \times 100$$

[0046]

表 7

被検化合物	濃 度	褪色抑制率 (%)
α-トコフェロール	0.1%	65
スクワレン	0.1%	60
コレステロール	0.1%	12
α-グルコシルルチン	0.1%	91
レチノール	0.1%	63
キノリン	0.1%	85
リノール酸	0.1%	20
オリーブ油	0.1%	5
なし (ブランク)		3

[0047] The tenebrescence of Orange II by the singlet oxygen which a rose bengal generates by light like [it is ***** and] from this result can be prevented if a velocity constant is more than 1.0x106M-1s-1.

[0048] Moreover, the brown of azo dye, such as Orange II, could be prevented, and also it turned out that it is effective also in tenebrescence [, such as a quinone system coloring matter; beet red,] of natural coloring matter, such as flavin coloring matter, such as a betacyanin system coloring matter; riboflavin, such as flavonoid; KERUMESU coloring matter, such as grape pericarp coloring matter and berries coloring matter, and alizarin coloring matter, and discoloration prevention.

[0049] Fruit ** Example 1 GE RU ** Fat: The gel ointment of the following formula was manufactured with the conventional method.

(Group **) (weight section)

A carboxyvinyl polymer 1.0 Triethanolamine 1.0 1, 3-butylene glycol 10.0 alpha-glucosyl rutin 0.01 Energy Make Water ** Amount ----- ** Total 100.0 [0050] Fruit ** Example 2 foundation : The foundation of the following formula was manufactured with the conventional method.

(Group **) (weight section)

Talc ** Amount A mica 40.0 Titanium oxide 10.0 Mica titanium 1.0 Red ochre 1.0 Yellow oxide of iron 1.8 liquid paraffins 4.0 Squalane 5.0 methyopolysiloxane 4.0 alpha-glucosyl rutin 0.01 Para methoxycinnamic acid 2-ethyl 0.1 Hexyl Hydroxy methoxybenzophenone 0.1 *** agent 0.2 Scent Charge 0.1 -----

** Total 100.0 [0051] Fruit ** Example 3 milk Liquid : The milky lotion of the following formula was manufactured with the conventional method.

(Group **) (weight section)

Squalane 5.0 Vaseline 2.0 Yellow bees wax 0.5 Sorbitan sesquioleic acid ether 0.4 Polyoxyethylene oleyl ether 1.2 (20E.O.)

1, 3-butylene glycol 5.0 alpha-glucosyl rutin 0.1 SOD 0.001 Ethyl alcohol 5.0 *** Agent 0.2 Scent Charge 0.1 Xanthan gum (20% water solution) 20.0 Energy Make Water ** Amount ----- ** Amount

100.0 [0052] Fruit ** Example Four-izing ** Water : The face toilet of the following formula was manufactured with the conventional method.

(Group **) (weight section)

A glycerol 5.0 A 1, 3-butylene glycol 6.5 Polyoxyethylene sorbitan Mono-lauric-acid ester (20E.O.) 1.2 Ethyl alcohol 8.0 A hypotaurine 1.0 ** ** Agent 0.2 Scent Charge 0.1 energy Make Water ** Amount ----- ** Amount 100.0 [0053] Fruit ** Example 5 ** ** Agent : The cleaning agent of the following formula was manufactured with the conventional method.

(Group **) (weight section)

Stearin acid 10.0 A palmitic acid 8.0 A myristic acid 12.0 A lauric acid 4.0 Oleyl alcohol 1.5 Purified lanolin 1.0 Scent Charge 0.1 ** ** Agent 0.2 Glycerol 18.0 A calcium hydroxide 6.0 Thiotaurine 1.0 Energy Make Water ** Amount ----- ** Amount 100.0 [0054] Fruit ** Example Six creams : The cream of the following formula was manufactured with the conventional method.

(Group **) (weight section)

Yellow bees wax 6.0 Cetanol 5.0 Reduction lanolin 5.0 Squalane 30.0 Glycerol monostearate 4.0

Polyoxyethylene sorbitan Mono-lauric-acid ester (20E.O.) 2.0 Phosphatidylcholine 0.5

phosphatidylethanolamine 0.5 ** ** Agent 0.3 scents Charge 0.1 Energy Make Water ** Amount -----

----- ** Amount 100.0 [0055] There is the singlet oxygen elimination effectiveness, melanism is controlled instancy, and the gel ointment of the above example 1 and the charge of makeup of examples 2-6 are effective for aging prevention. Especially in the charge of makeup of an example 3, erythema control was accepted according to concomitant use with SOD, and it also had the anti-inflammation effectiveness.

[0056]

[Effect of the Invention] The external preparations of this invention can control various kinds of failures caused by singlet oxygen in the living body, for example, arch forming of a collagen, deactivation of the enzyme of versatility melanism and in the living body instancy produced by oxidation of dopa, the tenebrescence of coloring matter, etc., and can prevent degraded phenomena, such as the skin. therefore, the external preparations of this invention -- a collagen bridge formation inhibitor and instancy -- melanism -- it can be used in favor of skin external preparations, cosmetics, etc. as an inhibitor, an enzyme deactivation inhibitor, or a coloring matter tenebrescence inhibitor.

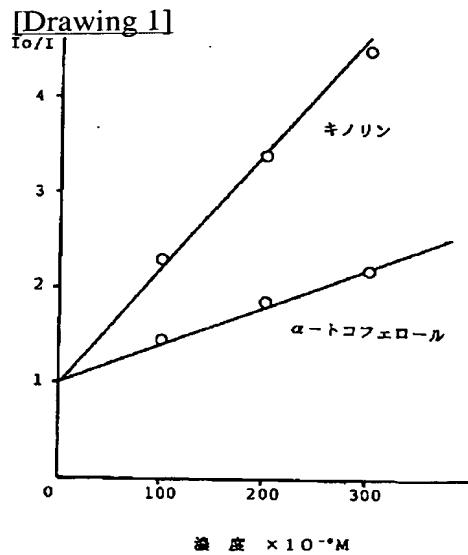
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DRAWINGS



[Translation done.]

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[Filing Date] September 18, Heisei 8

[Procedure amendment 1]

[Document to be Amended] Specification

[Item(s) to be Amended] Whole sentence

[Method of Amendment] Modification

[Proposed Amendment]

[Document Name] Specification

[Title of the Invention] External preparations

[Claim(s)]

[Claim 1] External preparations chosen from the collagen bridge formation inhibitor or coloring matter tenebrescence inhibitor which contains the compound whose velocity constant with singlet oxygen is more than $1 \times 10^6 M^{-1} s^{-1}$ as an active principle.

[Claim 2] Furthermore, external preparations given [containing an ultraviolet ray absorbent] in the 1st term of a claim.

[Claim 3] The 1st term of a claim which is a charge of makeup, or external preparations given in the 2nd term.

[Detailed Description of the Invention]

[0001]

[Industrial Application] About external preparations, in more detail, by preventing the arch-forming reaction of a collagen etc., this invention controls aging and relates to the external preparations used as cosmetics or physic.

[0002]

[Description of the Prior Art] In recent years, various diseases by active oxygen attract attention, and active oxygen has been said whether to involve also to aging. Super oxide, a hydroxy radical, a hydrogen peroxide, and singlet oxygen are contained in active oxygen, and the resultant with these metals and lipids is also known as active oxygen of a wide sense.

[0003] Various external preparations are studied in order to prevent various diseases in which active oxygen participates. For example, although the collagen which is a dermis constituent is bearing the resiliency of the skin, and flexibility, if bridge formation is formed in this collagen, resiliency and flexibility will fall, it is supposed that it is the cause of aging of the skin, and the collagen bridge formation inhibitor for preventing such a phenomenon is examined.

[0004] Furthermore, although the tenebrescence of coloring matter, such as vegetable extractives, or discoloration included in the charge of makeup etc. may become the stability top problem of cosmetics and this cause is set to light, temperature, and pH, explanation does not attach all so then and the drugs which prevent ** and discoloration of coloring matter are examined.

[0005] Although it was admitted that active oxygen was participating in the above-mentioned phenomena, such as collagen arch forming and coloring matter tenebrescence, it was not known about these actual cause or its

action mechanism, but, as for the compound effective in prevention of each [these] phenomenon, it was actual to have found out experientially and to have not spread.

[0006]

[Problem(s) to be Solved by the Invention] Therefore, it searched for causes including the action mechanism about the above-mentioned phenomenon, and offer of the external preparations which can prevent these phenomena was called for.

[0007]

[Means for Solving the Problem] Although each of these phenomena had very high reactivity among active oxygen as a result of this invention persons' examining synthetically what kind of active oxygen is involving about above-mentioned collagen arch forming, coloring matter tenebrescence, etc., the life was very short and its attention was paid to possibility that the singlet oxygen by which the concrete effect to a living body, for example, the skin, is not known is involving.

[0008] However, about singlet oxygen, he has noticed that the matter which there is no method of still detecting this correctly, cannot grasp relation of the various phenomena on the skin as singlet oxygen correctly, as a result eliminates this cannot be found out correctly.

[0009] Then, this invention persons inquired about the detection approach of singlet oxygen first, and developed new singlet oxygen detection equipment. Subsequently, as for the compound more than fixed, arch forming of the collagen which is the major component of dermis which is made into the failure by active oxygen in the living body, as a result leads to aging being too caused by singlet oxygen, when the matter which eliminates an operation of singlet oxygen and singlet oxygen with this detection equipment is searched, and a reaction constant with singlet oxygen completed a header and this invention for the ability of these failures to be controlled effectively.

[0010] That is, this invention offers the external preparations chosen from the collagen bridge formation inhibitor or coloring matter tenebrescence inhibitor which contains the compound whose velocity constant with singlet oxygen is more than $1 \times 10^6 M^{-1} s^{-1}$ as an active principle.

[0011] a velocity constant with the singlet oxygen used in this invention can excite a photosensitizer by the laser radiation of the equipment which these people developed, i.e., ultraviolet-rays wavelength, and can choose easily the compound beyond $1 \times 10^6 M^{-1} s^{-1}$ (henceforth a "singlet-oxygen elimination compound") by using the equipment (Japanese Patent Application No. No. 340377 [five to]) based on the principle of detecting near-infrared luminescence which the generated singlet oxygen gives off.

[0012] If it says in more detail, the laser of ultraviolet-rays wavelength can be irradiated at the system by which generating of the singlet oxygen by photochemical sensitization is known, fine luminescence of the specific near-infrared section can be measured to singlet oxygen, luminescence when subsequently adding a sample compound to the same system can be measured, it can ask for a velocity constant with singlet oxygen from reduction of the near-infrared section luminescence, and, thereby, a singlet oxygen elimination compound can be screened.

[0013] Calculation of a concrete velocity constant (kq) is the formula of these relation to Stern-Vormer for a Y-axis about ratio (I_0)[of luminescence reinforcement (I_0) when not adding the singlet oxygen elimination agent / as opposed to the luminescence reinforcement at that time (I) for the concentration (C_q) of a sample compound (singlet oxygen elimination agent) / to the X-axis $] / (I)$,

$$I_0/I = 1 + kq \cdot \tau \cdot C_q$$

What is necessary is to be alike and just to ask more. In this formula, τ is the life of singlet oxygen and is a constant which changes with solvents.

[0014] As an example of the singlet oxygen elimination compound found out by this approach, what is shown, for example in degree table is mentioned.

[0015]

[Table 1]

物質名	反応速度定数 (M ⁻¹ s ⁻¹)
β-カロチン	7.0×10 ⁹
α-グルコシルルチン	6.1×10 ⁹
ルチン	5.5×10 ⁹
ヒスチジン	5.4×10 ⁹
キノリン	1.0×10 ⁹
ドデシル硫酸ナトリウム	1.0×10 ⁹
アジ化ナトリウム	7.9×10 ⁸
α-トコフェロール	7.1×10 ⁸
クロロフィルa	7.0×10 ⁸
ドーパ	6.8×10 ⁸
β-トコフェロール	3.6×10 ⁸
トリプトファン	2.5×10 ⁸
γ-トコフェロール	1.9×10 ⁸
カテキン	0.6~1.2×10 ⁸
ケルセチン	1.1×10 ⁸
ケルセチン脂肪酸エステル	5~8×10 ⁷
δ-トコフェロール	7.1×10 ⁷
ハイドロキノン	6.9×10 ⁷
ナフトール	0.7~3.2×10 ⁷
ルミノール	3.0×10 ⁷
チロシン	2.7×10 ⁷
メチオニン	2.2×10 ⁷
プロアントシアニジン	1.0~2.1×10 ⁷
システィン	1.8×10 ⁷
ビリルビン	1.5×10 ⁷

オレイン酸	1.3×10^5
インデン	6.7×10^4
コレステロール	6.6×10^4
リモネン	5.9×10^4
安息香酸	5.0×10^4
マンニトール	1.8×10^4

[0016] The external preparations of this invention are manufactured by combining the singlet oxygen elimination compound found out as mentioned above, the well-known basis for ***** agents, or the basis for cosmetics according to a conventional method.

[0017] Generally the loadings of a singlet oxygen elimination compound are 0.0001% - 10% during a presentation, although it changes also with reaction reinforcement with the singlet oxygen of a singlet oxygen elimination compound besides being the dosage forms of external preparations, the purpose of use, etc. What is necessary is just to be 0.001% - about 1% preferably.

[0018] Concretely, the desirable loadings range by the application of a singlet oxygen elimination compound and external preparations is illustrated to the next Table 2 and 3.

[0019]

[Table 2]

化 合 物 名	コラーゲン架橋 抑制効果
α-グルコシル ルチン	0.1~1
ドデシル硫酸 ナトリウム	0.01~0.1
アジ化ナトリ ウム	0.5~2
ドーパ	0.1~1
アントシアニン	0.1~1
メチオニン	1~5
チロシン	1~5
システイン	1~5
ヒスチジン	0.01~0.1
トリプトファン	0.05~0.2
カテキン	0.1~1
ハイドロキノン	1~5
プロアント シアニジン	1~5
アスコルビン酸	1~5
チオタウリン	2~10
ヒポタウリン	2~10

(単位は重量%)

[0020]
 [Table 3]

化 合 物 名	色 素 褪 色 抑制効果
β-カロチン	0.01~0.1
ルチン	0.01~0.1
キノリン	0.01~0.1
クロロフィルa	0.01~0.2
α-トコフェロール	0.01~0.5
β-トコフェロール	0.01~0.5
γ-トコフェロール	0.01~0.5
δ-トコフェロール	0.01~0.5
ケルセチン	0.01~0.5
ケルセチン脂肪酸エステル	0.01~0.5
ハイドロキノン	0.05~5
ナフトール	0.05~5
ルミノール	0.05~5
ビリルビン	0.05~5
エルゴステロール	0.05~5
レチノール	0.1~5
ホスファチジルコリン	0.1~5
スクワレン	0.1~5
ホスファチジル エタノールアミン	0.1~5
酢酸トコフェロール	0.1~5

(単位は重量%)

[0021] The aquosity component and powder which are used for a usual ***** agent and the usual charge of makeup if needed, a surfactant, oils, a moisturizer, alcohols, pH regulator, antiseptics, coloring matter, an

antioxidant, a thickener, perfume, etc. can be further blended with the external preparations of this invention suitably, and it can consider as dosage forms, such as a milky lotion, a cream, face toilet, a pack, ointment, dispersion liquid, and a charge of washing.

[0022] As for the external preparations of this invention, combining with an ultraviolet ray absorbent is desirable, and Para methoxycinnamic acid 2-ethyl ester, 2-hydroxy-4-methoxybenzophenone, 4-t-butyl-4'-methoxydibenzoylmethane, hydroxy methoxybenzophenone sulfonic-acid sodium, etc. are mentioned as an example of such an ultraviolet ray absorbent. Among these, what has big absorption especially in UV-area A, for example, 4-t-butyl-4'-methoxydibenzoylmethane, hydroxy methoxybenzophenone sulfonic-acid sodium, etc. are desirable.

[0023] The external preparations obtained by the above can eliminate effectively the singlet oxygen generated on a living body, especially the skin, and are used as a collagen bridge formation inhibitor, a tenebrescence inhibitor of coloring matter, etc.

[0024]

[Example] Next, although the example of a trial and an example are given and this invention is explained in more detail, this invention is not restrained at all by the example of these trials etc.

[0025] Trial ** Example 1

Measuring method of singlet oxygen :

The measuring device of [measuring device []] singlet oxygen was constituted as follows.

(1) Light source section :

The argon laser by the coherent (Coherent) company (Innova 70-4)

(2) Intensity modulation section :

IntraAction (IntraAction) acoustooptic modulator

(ASM-702-8,ME-70)

(3) Flow cell :

The flow cell made from a quartz (cel length 3mm; capacity 0.18ml)

[0026]

(4) The pump for circulation, and bubbling equipment :

Peri SUTARU theque pump by the Iwaki glass company TST-100

High-pressure-oxygen chemical cylinder

(5) A light filter, a spectroscope, and detector :

Colored glass filter (IR-80)

The spectroscope by Jasco Corp. (CT-10, slit width of 2mm)

germanium[by the applied detector (Applied Detector) company]-detector

- (Model 403 HS; liquid nitrogen cooling)

(6) Amplifier

EG & G Pudding SETON applied research (EG & G Princeton)

Lock in amplifier made from Applied Research (Model(s) 124A and 116)

[0027] As a [measuring method []] test portion, it is hematoporphyrin. 20microM solution was used. This hematoporphyrin solution was circulated at the rate of 20 ml/min among the flow cell.

[0028] Laser with a wavelength (absorption maximum wavelength of hematoporphyrin) of 350-365nm was irradiated at this cel. When this exposure investigated the emission spectrum of the near infrared region to produce, it checked that a peak was in 1268nm. This peak corresponds to transition of an excitation singlet oxygen molecule.

[0029] Subsequently, when the concentration of hematoporphyrin was changed and the luminescence reinforcement of 1268nm was investigated, in low concentration, getting on a straight line mostly was checked and it checked that this luminescence was what is depended on the singlet oxygen generated when hematoporphyrin is made into a photosensitizer.

[0030] Trial ** Example 2

The measurement trial of a reaction rate constant: The reaction rate constant was measured using the rose bengal which is a typical photosensitizer, the alpha-tocopherol as an elimination compound, and each ethanol solution of a quinoline. Laser light was irradiated at each alpha-tocopherol of the rose bengal of 50microM, and 0,100,200,300,400microM, and the mixed solution of a quinoline, and the luminescence reinforcement in

1268nm was measured.

[0031] As shown in drawing 1, the concentration (Cq) of an elimination compound is taken along an axis of abscissa, and Io/I (luminescence reinforcement in each concentration when luminescence reinforcement in case the elimination compound of Io is 0, and I add an elimination compound) is taken along an axis of ordinate, and it is the formula of Stern-Vormer,

$$Io/I = 1 + kq \cdot \tau \cdot Cq$$

It was alike, and it followed and kq (velocity constant) was calculated from the inclination of the obtained graph. In addition, the life (τ) of the singlet oxygen in the inside of ethanol is 10-12microsec.

[0032] Trial ** Example 3

Depressant action of arch forming of a collagen: Add 200microM hematoporphyrin 100microl to about 1mg/ml I-beam collagen 200microl, and add 50 mM Tris-HCl buffer solution so that the whole quantity may be further set to 1ml. This is taken on a petri dish and UV-A 2 mW/cm² is irradiated for 20 minutes by the solar simulator. Under the present circumstances, reaction mixture is ice-cooled and stirred.

[0033] The sample before and behind a UV-A exposure is separated in SDS-PAGE, and change of the amount of alpha of a collagen, beta, and a gamma chain is seen. It compared by the case where variation of alpha of this collagen, beta, and a gamma chain is not added with the case where a sample compound (singlet oxygen elimination compound) is added, and that operation was investigated. This result is shown in the following table.

[0034]

[Table 4]

被検化合物	濃 度	コラーゲンの変化程度
α -グルコシルルチン	0.1 %	UV-A 照射前と比べ変化なし
チオタウリン	5 %	同 上
ヒポタウリン	5 %	同 上
ドデシル硫酸ナトリウム	0.1 %	同 上
カテキン	0.1 %	同 上
アジ化ナトリウム	0.5 %	同 上
マンニトール	1 %	高分子側の γ 鎖バンドが増え、架橋形成が示された
安息香酸	1 %	同 上
なし (ブランク)		同 上

[0035] When a singlet oxygen elimination compound was added like [it is ***** and] from this result, it was shown that arch forming of a collagen is controlled.

[0036] Trial ** Example Four colors Base ** Color ** System Effect ** : Rose bengal 0.01% and Orange Orange after putting II 0.01% of coloring matter mixed liquor into Fl box for two weeks The absorbance of 484nm which shows the maximum absorption of II was measured, and it asked for whenever [tenebrescence / of Orange II]. Subsequently, the sample compound (singlet oxygen elimination compound) was added into the same coloring matter mixed liquor, whenever [tenebrescence / in this case] was measured, and the coloring matter tenebrescence depressor effect of a sample compound was investigated. This result is shown in the next table.

[0037] In addition, coloring matter tenebrescence depressor effect was searched for from the following formula.

The absorbance of 484nm after a trial
rate of tenebrescence control =----- x100

The absorbance of 484nm before a trial

[0038]

[Table 5]

被検化合物	濃 度	褪色抑制率 (%)
α-トコフェロール	0.1%	65
スクワレン	0.1%	60
コレステロール	0.1%	12
α-グルコシルルチン	0.1%	91
レチノール	0.1%	63
キノリン	0.1%	85
リノール酸	0.1%	20
オリーブ油 な し (プランク)	0.1% —	5 3

[0039] The tenebrescence of Orange II by the singlet oxygen which a rose bengal generates by light like [it is ***** and] from this result can be prevented if a velocity constant is more than $1.0 \times 10^6 M^{-1}s^{-1}$.

[0040] Moreover, the brown of azo dye, such as Orange II, could be prevented, and also it turned out that it is effective also in tenebrescence [, such as a quinone system coloring matter; beet red,] of natural coloring matter, such as flavin coloring matter, such as a betacyanin system coloring matter; riboflavin, such as flavonoid; KERUMESU coloring matter, such as grape pericarp coloring matter and berries coloring matter, and alizarin coloring matter, and discoloration prevention.

[0041] Fruit ** Example 1

GE RU ** Fat: The gel ointment of the following formula was manufactured with the conventional method.

(Group **) (weight section)

Carboxyvinyl polymer 1.0

Triethanolamine 1.0
 1, 3-butylene glycol 10.0
 alpha-glucosyl rutin 0.01
 Energy Make Water ** Amount

** Total 100.0

[0042] Fruit ** Example 2

Foundation : the foundation of the following formula was manufactured with the conventional method.
 (Group **) (weight section)

Talc ** Amount

Mica 40.0

Titanium oxide 10.0

Mica titanium 1.0

Red ocher 1.0

Yellow oxide of iron 1.8

Liquid paraffin 4.0

Squalane 5.0

Methyopolysiloxane 4.0

alpha-glucosyl rutin 0.01

Para methoxycinnamic acid 2-ethyl 0.1

Hexyl

Hydroxy methoxybenzophenone 0.1

*** Agent 0.2

Scent Charge 0.1

** Total 100.0

[0043] Fruit ** Example 3

Milk Liquid : The milky lotion of the following formula was manufactured with the conventional method.
 (Group **) (weight section)

Squalane 5.0

Vaseline 2.0

Yellow bees wax 0.5

Sorbitan sesquioleic acid ether 0.4

Polyoxyethylene oleyl ether 1.2

(20E.O.)

1, 3-butylene glycol 5.0

alpha-glucosyl rutin 0.1

SOD 0.001

Ethyl alcohol 5.0

*** Agent 0.2

Scent Charge 0.1

Xanthan gum (20% water solution) 20.0

Energy Make Water ** Amount

** Amount 100.0

[0044] Fruit ** Example 4

*** Water : The face toilet of the following formula was manufactured with the conventional method.
 (Group **) (weight section)

Glycerol 5.0

1, 3-butylene glycol 6.5

Polyoxyethylene sorbitan

Mono-lauric-acid ester (20E.O.) 1.2

Ethyl alcohol 8.0

Hypotaurine 1.0
 *** Agent 0.2
 Scent Charge 0.1
 Energy Make Water ** Amount

** Amount 100.0

[0045] Fruit ** Example 5

*** Agent : The cleaning agent of the following formula was manufactured with the conventional method.
 (Group **) (weight section)

Stearin acid 10.0

Palmitic acid 8.0

Myristic acid 12.0

Lauric acid 4.0

Oleyl alcohol 1.5

Purified lanolin 1.0

Scent Charge 0.1

*** Agent 0.2

Glycerol 18.0

Calcium hydroxide 6.0

Thiotaurine 1.0

Energy Make Water ** Amount

** Amount 100.0

[0046] Fruit ** Example 6

Cream : the cream of the following formula was manufactured with the conventional method.
 (Group **) (weight section)

Yellow bees wax 6.0

Cetanol 5.0

Reduction lanolin 5.0

Squalane 30.0

Glycerol monostearate 4.0

Polyoxyethylene sorbitan

Mono-lauric-acid ester (20E.O.) 2.0

Phosphatidylcholine 0.5

Phosphatidylethanolamine 0.5

*** Agent 0.3

Scent Charge 0.1

Energy Make Water ** Amount

** Amount 100.0

[0047] The gel ointment of the above example 1 and the charge of makeup of examples 2-6 have the singlet oxygen elimination effectiveness, and are effective for aging prevention. Especially in the charge of makeup of an example 3, erythema control was accepted according to concomitant use with SOD, and it also had the anti-inflammation effectiveness.

[0048]

[Effect of the Invention] The external preparations of this invention can control various kinds of failures caused by singlet oxygen in the living body, for example, arch forming of a collagen, the tenebrescence of coloring matter, etc., and can prevent degraded phenomena, such as the skin. Therefore, the external preparations of this invention can be used in favor of skin external preparations, cosmetics, etc. as a collagen bridge formation inhibitor or a coloring matter tenebrescence inhibitor.

[Brief Description of the Drawings]

[Drawing 1] The drawing in which the graph for asking for a velocity constant with singlet oxygen is shown.

[Translation done.]

EXTERNAL PREPARATION

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Publication date: 1995-09-05
Inventor: KAMEYAMA HISAMI; MASUNAGA TAKUJI; RYU AKIYOSHI
Applicant: KOSE CORP
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Application number: JP19940333581 19941216
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Abstract of JP7233046

PURPOSE: To obtain an external preparation, containing a specific compound eliminating single oxygen, capable of preventing collagen from causing the cross-linkage-forming reaction, the instantaneous blackening from occurring, enzymes from being inactivated, etc., and thereby suppressing the aging and utilizable as cosmetics and medicines. **CONSTITUTION:** This external preparation is obtained by blending a compound such as alpha-glucosylrutin, hypotaurine, thiotaureine or phosphatidyl-choline having $\geq 1 \times 10^{-6}$ mol \cdot sec $^{-1}$ rate constant of reaction with single oxygen in an amount of 0.0001-10% (preferably 0.001-1%) therein. Furthermore, the external preparation is preferably combined with an ultraviolet light absorber such as 4-t-butyl-4'-methoxydibenzoylmethane or sodium hydroxymethoxybenzophenonesulfonate.

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(54)【発明の名称】 外用剤

(57)【要約】

【構成】 一重項酸素との反応速度定数が $1 \times 10^6 M^{-1} s^{-1}$ 以上である化合物を有効成分として含有する、コラーゲン架橋抑制剤、即時黒化抑制剤、酵素失活抑制剤または色素褪色防止剤から選ばれる外用剤。

【効果】 本発明の外用剤は、生体内で一重項酸素により引き起こされる各種の障害、例えばコラーゲンの架橋形成、ドーパの酸化により生じる即時黒化、生体内的種々の酵素の失活、色素の褪色等を抑制し、皮膚等の老化現象を防ぐことができるものであり、コラーゲン架橋抑制剤、即時黒化抑制剤、酵素失活抑制剤または色素褪色防止剤などとして、皮膚外用剤、化粧品等に有利に使用できるものである。

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【特許請求の範囲】

【請求項1】 一重項酸素との反応速度定数が $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ 以上である化合物を有効成分として含有する、コラーゲン架橋抑制剤、即時黒化抑制剤、酵素失活抑制剤または色素褪色防止剤から選ばれる外用剤。

【請求項2】 更に紫外線吸収剤を含有する請求項第1項記載の外用剤。

【請求項3】 化粧料である請求項第1項または第2項記載の外用剤。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、外用剤に関し、更に詳しくは、コラーゲンの架橋形成反応や即時黒化、酵素不活性化等を防止し、ひいては老化を抑制し、化粧品や医薬として利用される外用剤に関する。

【0002】

【従来の技術】近年、活性酸素による様々な疾患が注目されており、老化にも活性酸素が、関与しているのではないかと言われてきている。活性酸素には、スーパーオキサイド、ヒドロキシラジカル、過酸化水素および一重項酸素が含まれており、また、これらの金属や脂質との反応生成物も広義の活性酸素として知られている。

【0003】活性酸素が関与する様々な疾患を防ぐ目的で、種々の外用剤が研究されている。例えば、真皮構成成分であるコラーゲンは、皮膚の弾力性、柔軟性を担っているが、このコラーゲンに架橋が形成されると弾力性、柔軟性が低下し、皮膚の老化の一因であるとされており、このような現象を防ぐためのコラーゲン架橋抑制剤が検討されている。また、紫外線による黒化には、UV-Bによる遅延型黒化の他、UV-Aによる即時黒化の存在が知られており、このような黒化を防ぐための即時黒化抑制剤が検討されている。

【0004】更に、生体内反応を担っている数多くの酵素は、老化の進行と共に失活する割合が高くなり、その修復が困難になること知られており、これらの酵素の失活を防ぐための酵素失活抑制剤が検討されている。更にまた、化粧料等に含まれる植物エキス等の色素の褪色あるいは変色は、化粧品の安定性上問題になることがある。この原因は光、温度、pHとされているが、それだけではすべて説明がつくわけではなく、色素の褪・変色を防止する薬剤が検討されている。

【0005】上記の、コラーゲン架橋形成、即時黒化、酵素失活および色素褪色等の現象には、活性酸素が関与していることは認められているものの、これらの実際の原因やその作用機序については知られておらず、これら各現象の防止に有効である化合物は、経験的に見い出すしかないので現実であった。

【0006】

【発明が解決しようとする課題】従って、上記現象について、その作用機序を含め原因を探求し、これら現象を

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防ぐことのできる外用剤の提供が求められていた。

【0007】

【課題を解決するための手段】本発明者らは、上記のコラーゲン架橋形成、即時黒化、酵素失活および色素褪色等に関し、どのような活性酸素が関与しているかを総合的に検討した結果、これらの現象は、いずれも活性酸素のうち、反応性が非常に高いが、寿命の極めて短く、生体、例えば皮膚に対する具体的な影響が知られていない一重項酸素が関与している可能性に着目した。

10 【0008】しかし、一重項酸素については、未だこれを正確に検出する方法がなく、この結果、一重項酸素と皮膚上の種々の現象の関係を正確に把握できず、ひいてはこれを消去する物質を正しく見出すことができないことに気付いた。

【0009】そこで、本発明者らはまず一重項酸素の検出方法について研究を行い、新しい一重項酸素検出装置を開発した。次いで、この検出装置により一重項酸素の作用および一重項酸素を消去する物質を検索したところ、生体内での活性酸素による障害とされ、ひいては老化につながる、真皮の主要成分であるコラーゲンの架橋形成、ドーパの酸化により非酵素的に起こる即時黒化、生体に必須の種々の酵素の失活等はやはり一重項酸素により引き起こされていること、および一重項酸素との反応速度定数が一定以上の化合物は、これらの障害を有効に抑制できることを見出し、本発明を完成した。

20 【0010】すなわち本発明は、一重項酸素との反応速度定数が $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ 以上である化合物を有効成分として含有する、コラーゲン架橋抑制剤、即時黒化抑制剤、酵素失活抑制剤または色素褪色防止剤から選ばれる外用剤を提供するものである。

【0011】本発明において使用される一重項酸素との反応速度定数が $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ 以上の化合物（以下、「一重項酸素消去化合物」という）は、本出願人らの開発した装置、すなわち、紫外線波長のレーザー照射によって光増感剤を励起し、発生した一重項酸素が出す近赤外発光を検出するという原理に基づく装置（特願平5-340377号）を利用することにより容易に選択することができる。

30 【0012】より詳しくいえば、光増感反応による一重項酸素の発生が知られている系に紫外線波長のレーザーを照射し、一重項酸素に特異的な近赤外部の微発光を測定し、次いで、同じ系に被検化合物を加えた時の発光を測定し、その近赤外部発光の減少から一重項酸素との反応速度定数を求め、これにより一重項酸素消去化合物をスクリーニングすることができる。

40 【0013】具体的な反応速度定数 (k_q) の算出は、被検化合物（一重項酸素消去剤）の濃度 (C_q) をX軸に、そのときの発光強度 (I) に対する一重項酸素消去剤を加えてなかった時の発光強度 (I_0) の比 (I_0 / I) をY軸にとり、これらの関係から Stern-V

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ormerの式、
 $I_0/I = 1 + k_q \cdot \tau \cdot C_q$

により求めれば良い。この式において、 τ は一重項酸素の寿命であり溶媒によって異なる定数である。

表 1

* 【0014】この方法により見出された一重項酸素消去化合物の例としては、例えば次表に示すものが挙げられる。

* 【0015】

物質名	反応速度定数 (M ⁻¹ s ⁻¹)
β-カロチン	7.0 × 10 ⁹
α-グルコシルルチン	6.1 × 10 ⁹
ルチン	5.5 × 10 ⁹
ヒスチジン	5.4 × 10 ⁹
キノリン	1.0 × 10 ⁹
ドデシル硫酸ナトリウム	1.0 × 10 ⁹
アジ化ナトリウム	7.9 × 10 ⁸
α-トコフェロール	7.1 × 10 ⁸
クロロフィルa	7.0 × 10 ⁸
ドーパ	6.8 × 10 ⁸
β-トコフェロール	3.6 × 10 ⁸
トリプトファン	2.5 × 10 ⁸
γ-トコフェロール	1.9 × 10 ⁸
カテキン	0.6 ~ 1.2 × 10 ⁸
ケルセチン	1.1 × 10 ⁸
ケルセチン脂肪酸エステル	5 ~ 8 × 10 ⁷
δ-トコフェロール	7.1 × 10 ⁷
ハイドロキノン	6.9 × 10 ⁷
ナフトール	0.7 ~ 3.2 × 10 ⁷
ルミノール	3.0 × 10 ⁷
チロシン	2.7 × 10 ⁷
メチオニン	2.2 × 10 ⁷
プロアントシアニジン	1.0 ~ 2.1 × 10 ⁷
システイン	1.8 × 10 ⁷
ビリルビン	1.5 × 10 ⁷
エルゴステロール	1.3 × 10 ⁷
アスコルビン酸	8.3 × 10 ⁶
レチノール	7.3 × 10 ⁶
チオタウリン	1.1 ~ 2.3 × 10 ⁶
ホスファチジルコリン	2.1 × 10 ⁶
ヒポタウリン	1.0 ~ 2.0 × 10 ⁶
スクワレン	1.9 × 10 ⁶
ホスファチジルエタノールアミン	1.6 × 10 ⁶
酢酸トコフェロール	1.6 × 10 ⁶
アントラセン	7.4 × 10 ⁵
ビベリジン	4.1 × 10 ⁵
ドコサヘキサエン酸	2.9 × 10 ⁵
リノール酸	2.2 × 10 ⁵
オリーブ油	1.5 × 10 ⁵

5	オレイン酸 インデン コレステロール リモネン 安息香酸 マンニトール	6	1.3×10^5 6.7×10^4 6.6×10^4 5.9×10^4 5.0×10^4 1.8×10^4
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【0016】本発明の外用剤は、上記の様にして見出された一重項酸素消去化合物と公知の外用医剤用基剤または化粧品用基剤とを常法に従って組合せることにより製造される。

【0017】一重項酸素消去化合物の配合量は、外用剤の剤形、使用目的等の他、一重項酸素消去化合物の一重項酸素との反応強度によっても異なるが、一般には組成*

* 中0.0001%~10% 好ましくは0.001%~1%程度とすれば良い。

10 【0018】具体的に、一重項酸素消去化合物と外用剤の用途による配合量範囲を次の表2および表3に例示する。

【0019】

表 2

化 合 物 名	即 時 黒 化 抑 制 効 果	コ ラ ー ジ ン 架 構 抑 制 効 果	酵 素 失 活 抑 制 効 果
α-グルコシリル ルチン	0.01~0.1	0.1~1	0.1~1
ドデシル硫酸 ナトリウム	0.01~0.1	0.01~0.1	0.01~0.1
アジ化ナトリ ウム	0.1~1	0.5~2	0.5~2
ドーバ	—	0.1~1	0.1~1
アントシアニン	0.1~1	0.1~1	0.1~1
メチオニン	1~5	1~5	1~5
チロシン	1~5	1~5	1~5
システイン	1~5	1~5	1~5
ヒスチジン	0.01~0.1	0.01~0.1	0.5~2
トリプトファン	0.05~0.2	0.05~0.2	0.5~2
カテキン	0.1~1	0.1~1	0.1~5
ハイドロキノン	1~5	1~5	1~5
プロアント シアニジン	1~5	1~5	1~5
アスコルビン酸	1~5	1~5	1~5
チオタウリン	1~5	2~10	2~10
ヒポタウリン	1~5	2~10	2~10

(単位は重量%)

※ ※【0020】

表 3

化 合 物 名	色 素 褪 色 抑 制 効 果
β-カロチン	0.01~0.1
ルチン	0.01~0.1
キノリン	0.01~0.1
クロロフィルa	0.01~0.2
α-トコフェロール	0.01~0.5
β-トコフェロール	0.01~0.5
γ-トコフェロール	0.01~0.5
δ-トコフェロール	0.01~0.5
ケルセチン	0.01~0.5
ケルセチン脂肪酸エステル	0.01~0.5
ハイドロキノン	0.05~5
ナフトール	0.05~5
ルミノール	0.05~5
ビリルビン	0.05~5
エルゴステロール	0.05~5
レチノール	0.1~5
ホスファチジルコリン	0.1~5
スクワレン	0.1~5
ホスファチジル	0.1~5
エタノールアミン	
酢酸トコフェロール	0.1~5

(単位は重量%)

【0021】本発明の外用剤には、更に、必要に応じて通常の外用医剤や化粧料に用いられる水性成分、粉末、界面活性剤、油剤、保湿剤、アルコール類、pH調整剤、防腐剤、色素、酸化防止剤、増粘剤、香料等を適宜配合することができ、乳液、クリーム、化粧水、パック、軟膏、分散液、洗浄料等の剤形とすることができます。

【0022】本発明の外用剤は、紫外線吸収剤と組み合わせることが好ましく、このような紫外線吸収剤の具体例としては、バラメトキシケイ皮酸2-エチルエステル、2-ヒドロキシ-4-メトキシベンゾフェノン、4-t-ブチル-4'-メトキシジベンゾイルメタン、ヒドロキシメトキシベンゾフェノンスルホン酸ナトリウム等が挙げられる。このうち、特にUV-A領域に大きな吸収を有するもの、例えば4-t-ブチル-4'-メトキシジベンゾイルメタン、ヒドロキシメトキシベンゾフェノンスルホン酸ナトリウム等が好ましい。

【0023】以上により得られる外用剤は、生体、特に皮膚に発生する一重項酸素を有効に消去でき、コラーゲン架橋抑制剤、即時黒化抑制剤、酵素失活抑制剤、色素の褪色抑制剤等として利用される。

【0024】このうち、即時黒化抑制剤として使用する*

30 * 場合は、一重項酸素消去化合物として、反応速度定数がドーバより大きいこと (6.8×10^8 以上であること) がより好ましいが、ドーバより反応速度定数が小さい化合物であっても、高濃度添加することにより同様な効果を得ることができる。また、酵素の失活抑制剤として利用する場合は、その酵素の反応速度定数より一重項酸素消去化合物の反応定数が大きいことがより好ましい。

【0025】

【実施例】次に、試験例および実施例を挙げ、本発明を更に詳しく説明するが、本発明はこれら試験例等になんら制約されるものではない。

40 【0026】試験例 1

一重項酸素の測定方法：

【測定装置】一重項酸素の測定装置は、次のように構成した。

(1) 光源部：コヒーレント (Coherent) 社製アルゴンレーザー (Innova 70-4)

(2) 強度変調部：イントラ・アクション (IntraAction) 社製音響光学変調器 (ASM-702-8, ME-70)

(3) フローセル：石英製フローセル (セル長 3 m
m; 容量 0.18 ml)

【0027】(4) 循環用ポンプおよびバーリング装

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置：岩城ガラス社製ペリスタルティクポンプ T S T -
1 0 0

高圧酸素ガスボンベ

(5) 可視光フィルター、分光器および検出器：色ガラスフィルター（IR-80）

日本分光社製分光器（CT-10、スリット幅2mm）

アプライド・デテクター（Applied Detector）社製Ge -ディテクター（Model 403 HS；液体窒素冷却）

(6) 増幅器

EG & G プリンセトン・アプライド・リサーチ（EG & G Princeton Applied Research）社製ロックインアンプ（Model 124A, 116）

【0028】[測定方法] 測定試料としては、ヘマトポルフィリンの20μM溶液を用いた。このヘマトポルフィリン溶液を、フローセル中、20ml/minの速度で循環させた。

【0029】このセルに、350～365nmの波長（ヘマトポルフィリンの極大吸収波長）のレーザーを照射した。この照射により、生ずる近赤外領域の発光スペクトルを調べたところ、1268nmにピークがあることを確認した。このピークは、励起一重項酸素分子の遷移に対応するものである。

【0030】次いで、ヘマトポルフィリンの濃度を変化させ、1268nmの発光強度を調べたところ、低濃度ではほぼ直線上にのることが確認され、この発光はヘマトポルフィリンを光増感剤としたときに発生する一重項酸素によるものであることを確認した。

【0031】試験例 2

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反応速度定数の測定試験：代表的な光増感剤であるローズベンガルと、消去化合物としてのα-トコフェロールおよびキノリンのそれぞれのエタノール溶液を用いて反応速度定数の測定を行った。50μMのローズベンガルと0、100、200、300、400μMの各α-トコフェロール及びキノリンの混合溶液にレーザー光を照射し、1268nmにおける発光強度を測定した。

【0032】図1に示すように、横軸に消去化合物の濃度（Cq）、縦軸にIo/I（Ioは消去化合物が0のときの発光強度、Iは消去化合物を添加したときの各濃度における発光強度）をとり、Stern-Vormerの式、

$$Io/I = 1 + kq \cdot \tau \cdot Cq$$

に従い、得られたグラフの傾きよりkq（反応速度定数）を求めた。なお、エタノール中での一重項酸素の寿命（τ）は10～12μsecである。

【0033】試験例 3

光酸化による即時黒化の抑制試験：まず、1mM ドーバと5μM ヘマトポルフィリンの混液（リン酸緩衝液；pH7.5）をシャーレに取り、ソーラーシミュレーターにてUV-A 5mW/cm²を10分間照射し、ドーバから変化したドーバクロムの生成を475nmの吸光度を測定することにより求めた。次いで、上記混液に一重項酸素消去化合物を添加し、UV-Aを照射したときのドーバクロムの生成を調べた。この結果を下表に示す。

【0034】

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表 4

一重項酸素消去化合物	濃 度	475 nmの吸光度
α-グルコシルルチン	0.05%	0.08
α-グルコシルルチン + ビトキシタキサンゾフェノン スルホン酸ナトリウム	0.05% + 0.01%	0.06
ヒスチジン	0.05%	0.1
ドデシル硫酸ナトリウム + ビトキシタキサンゾフェノン スルホン酸ナトリウム	0.1% + 0.01%	0.13
ドデシル硫酸ナトリウム	0.1%	0.17
ヒボタウリン	1%	0.2
マンニトール	1%	0.35
安息香酸	1%	0.32
な し (ブランク)		0.38

【0035】この結果から明らかなように、反応速度定数が $1 \times 10^6 M^{-1} s^{-1}$ より大きい一重項酸素消去化合物は、ドーバクロムの生成を抑制することから、即時黒化を抑制し、有効な一重項酸素消去剤となりうる。なお、上記各化合物は紫外線吸収剤と組み合わせることで、一重項酸素の発生を抑え、更に即時黒化抑制効果が高くなる。

【0036】試験例 4
コラーゲンの架橋形成の抑制作用：約 1 mg/ml の I 型コラーゲン 200 μl に 200 μM ヘマトポルフィリン 100 μl を加え、更に全量が 1 ml になるように 5 *

* 0 mM Tris-HCl 緩衝液を加える。これをシャーレに取り、ソーラーシミュレーターにて UV-A 2 mW/cm² を 20 分間照射する。この際、反応液は氷冷し、攪拌しておく。

【0037】UV-A 照射前後のサンプルを SDS-PAGE にて分離し、コラーゲンの α、β、γ 鎮の量の変化を見る。このコラーゲンの α、β および γ 鎮の変化量を、被検化合物（一重項酸素消去化合物）を添加した場合と添加しない場合で比較し、その作用を調べた。この結果を下表に示す。

【0038】

被検化合物	濃 度	コラーゲンの変化程度
α -グルコシルルチン 0.1%		UV-A照射前と比べ変化なし
チオタウリン 5 %		同 上
ヒポタウリン 5 %		同 上
ドデシル硫酸ナトリウム 0.1%		同 上
カテキン 0.1%		同 上
アジ化ナトリウム 0.5 %		同 上
マンニトール 1 %		高分子側の γ 鎖バンドが増え、架橋形成が示された
安息香酸 なし (ブランク)	1 %	同 上

【0039】この結果から明かなように、一重項酸素消去化合物を添加した場合、コラーゲンの架橋形成が抑制されることが示された。

【0040】試験例 5

酵素の失活の抑制 : 0.5 mg/ml チロシナーゼ溶液 3 ml に、200 μ M のヘマトボルフィリンを 300 μ l 加え、UV-A を一定時間照射した後、この酵素溶液 0.1 ml に 3.9 ml のリン酸緩衝液 (pH 6.8) を加える。

【0041】次いで、10 mM のドーバー 1 ml を基質 * 表 6

* とし、37 °C で 10 分間に生成するドーバクロムの量を 20 475 nm の吸光度で測定し、UV-A を照射しないものを対照として生成するドーバクロム量の低下からチロシナーゼ活性の低下を確認した。一方、被検化合物（一重項酸素消去剤）を加えて UV-A を照射した場合のチロシナーゼ活性を測定し、消去剤によるチロシナーゼ失活の抑制効果を調べた。この結果を、次表に示す。

【0042】

被検化合物	濃 度	残存活性 (%)
アジ化ナトリウム	0.5 %	98
α -グルコシルルチン	0.1 %	98
トリプトファン	1 %	97
チオタウリン	5 %	82
ヒポタウリン	5 %	85
マンニトール	1 %	45
安息香酸	1 %	39
なし (ブランク)		38

【0043】この結果から明らかのように、一重項酸素との反応定数が $1 \times 10^6 M^{-1} s^{-1}$ より大きいものが当該酵素の失活を抑制できる。

【0044】試験例 6

色素褪色抑制効果 : ローズベンガル 0.01% とオレンジ II 0.01% の色素混合液を F1 ボックスに 2 週間入れた後、オレンジ II の最大吸収を示す 48 *

※ 4 nm の吸光度を測定し、オレンジ II の褪色度を求めた。次いで、同様な色素混合液に被検化合物（一重項酸素消去化合物）を添加し、この場合の褪色度を比較し、被検化合物の色素褪色抑制効果を調べた。この結果を次の表に示す。

【0045】なお、色素褪色抑制効果は、次の式から求めた。

15

16

$$\text{褪色抑制率} = \frac{\text{試験後の } 484\text{ nm の吸光度}}{\text{試験前の } 484\text{ nm の吸光度}} \times 100$$

【0046】

表 7

被検化合物	濃 度	褪色抑制率 (%)
α-トコフェロール	0.1%	65
スクワレン	0.1%	60
コレステロール	0.1%	12
α-グルコシルルチン	0.1%	91
レチノール	0.1%	63
キノリン	0.1%	85
リノール酸	0.1%	20
オリーブ油	0.1%	5
なし (ブランク)		3

【0047】この結果から明かなように、光によりローズベンガルが発生する一重項酸素によるオレンジIIの褪色は、反応速度定数が $1.0 \times 10^6 M^{-1} s^{-1}$ 以上であれば防止することができる。

【0048】また、オレンジII等のアゾ色素の褐色を防ぐことができるほか、ブドウ果皮色素、ベリー類色素等のフラボノイド系色素；ケルメス色素、アリザリン色素*

* 等のキノン系色素；ビートレッド等のペタシアニン系色素；リボフラビン等のフラビン色素などの天然色素の褪色、変色防止にも有効であることがわかった。

【0049】実施例 1

ゲル軟膏：下記の処方のゲル軟膏を常法により製造した。

(組成)	(重量部)
カルボキシビニルポリマー	1.0
トリエタノールアミン	1.0
1,3-ブチレングリコール	10.0
α-グルコシルルチン	0.01
精製水	残量

合 計

100.0

【0050】実施例 2

※常法により製造した。

ファンデーション：下記の処方のファンデーションを※

(組成)	(重量部)
タルク	残量
マイカ	40.0
酸化チタン	10.0
雲母チタン	1.0
ベンガラ	1.0
黄酸化鉄	1.8
流動パラフィン	4.0
スクワラン	5.0
メチルポリシロキサン	4.0
α-グルコシルルチン	0.01
パラメトキシケイ皮酸 2-エチルヘキシリ	0.1
ヒドロキシメトキシベンゾフェノン	0.1
防腐剤	0.2

17

香 料

0.1

合 計

100.0

【0051】実施例3

(組成)

(重量部)

スクワラン	5.0
ワセリン	2.0
ミツロウ	0.5
ソルビタンセスキオレイン酸エーテル	0.4
ポリオキシエチレンオレイルエーテル	1.2
(20E.O.)	
1,3-ブチレングリコール	5.0
α-グルコシルルチン	0.1
SOD	0.001
エチルアルコール	5.0
防腐剤	0.2
香 料	0.1
キサンタンガム(20%水溶液)	20.0
精製水	残量

全 量

100.0

【0052】実施例4

※た。

化粧水：下記の処方の化粧水を常法により製造し※

(組成)

(重量部)

グリセリン	5.0
1,3-ブチレングリコール	6.5
ポリオキシエチレンソルビタン	
モノラウリン酸エステル(20E.O.)	1.2
エチルアルコール	8.0
ヒポタウリン	1.0
防腐剤	0.2
香 料	0.1
精製水	残量

全 量

100.0

【0053】実施例5

★た。

洗浄剤：下記の処方の洗浄剤を常法により製造し★

(組成)

(重量部)

ステアリン酸	10.0
パルミチン酸	8.0
ミリスチン酸	12.0
ラウリン酸	4.0
オレイルアルコール	1.5
精製ラノリン	1.0
香 料	0.1
防腐剤	0.2
グリセリン	18.0
水酸化カルシウム	6.0
チオタウリン	1.0
精製水	残量

全量	100.0
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*た。

【0054】実施例 6

クリーム：下記の処方のクリームを常法により製造し *

(組成)	(重量部)
ミツロウ	6.0
セタノール	5.0
還元ラノリン	5.0
スクワラン	30.0
グリセリンモノステアレート	4.0
ポリオキシエチレンソルビタン	
モノラウリン酸エステル(20E.O.)	2.0
ホスファチジルコリン	0.5
ホスファチジルエタノールアミン	0.5
防腐剤	0.3
香料	0.1
精製水	残量

全量	100.0
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【0055】以上の実施例1のゲル軟膏および実施例2～6の化粧料は一重項酸素消去効果があり、即時黒化が抑制され、老化予防に効果的なものである。特に実施例3の化粧料においてはSODとの併用により紅斑抑制が認められ、抗炎症効果も有していた。

【0056】

【発明の効果】本発明の外用剤は、生体内で一重項酸素により引き起こされる各種の障害、例えばコラーゲンの架橋形成、ドーパの酸化により生じる即時黒化、生体内

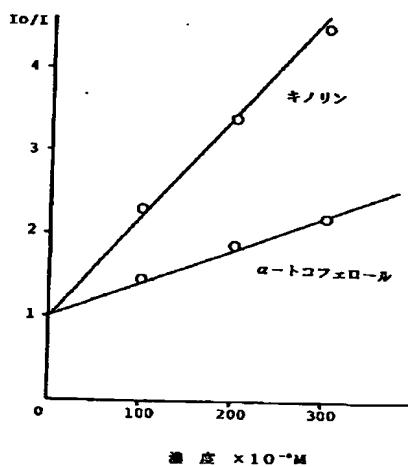
20※の種々の酵素の失活、色素の褪色等を抑制し、皮膚等の老化現象を防ぐことができるものである。従って、本発明の外用剤は、コラーゲン架橋抑制剤、即時黒化抑制剤、酵素失活抑制剤または色素褪色防止剤などとして、皮膚外用剤、化粧品等に有利に使用できるものである。

【図面の簡単な説明】

【図1】一重項酸素との反応速度定数を求めるためのグラフを示す図面。

以上

【図1】



フロントページの続き

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